Development of a Tissue Plasminogen Activator Installed Redox-ActiveNanoparticle (t-PA@iRNP) for Novel Therapeutics

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新しい治療を目指した組織プラスミノーゲン活性化剤を導入した酸化還元活性ナノ粒子（t-PA @ iRNP）の開発

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論　　文　　の　　要　　旨

This thesis aims to design a tissue plasminogen activator installed redox-active nanoparticle (t-PA@iRNP) for oxidative stress associated diseases, including ischemia-reperfusion injury and cancer therapeutics. The thesis is composed of five chapters. Summaries of each chapter are described as follows.

Chapter 1 described general introduction of the present thesis concerning the disordered oxidative stress associated diseases especially ischemia-reperfusion injury and cancer. t-PA as the only one thrombolytic agent, the drawback of which and issues of ROS scavenging is described in detail. In order to overcome the shortcomings of t-PA and traditional antioxidant, t-PA@iRNP system in this thesis is also summarized.

Chapter 2 describes synthesis of poly(ethylene glycol)-*b*-poly[4-(2,2,6,6-tetramethylpiperidine-1-oxyl) aminomethylstryrene] (PEG-*b*-PMNT) redox block copolymer in detail and preparation of t-PA installed nitroxide radical-containing, self-assembled nanoparticles (t-PA@iRNP). t-PA@iRNP showed high colloidal stability under physiological environment because of the strong hydrophobicity of the PMNT segment.

Chapter 3 describes the therapeutic effect of t-PA@iRNP through synergistic effect of thrombolysis and antioxidant effects in ischemic stroke. t-PA@iRNP significantly suppressed increases in cerebral infarct volume and improved neurological deficit after brain ischemia. In addition, t-PA-induced subarachnoid hemorrhage was also suppressed by t-PA@iRNP treatment through elimination of overproduced ROS.

Chapter 4 describes the therapeutic effect of t-PA@iRNP in colon cancer via synergistic effect of fibrinolysis and antioxidant effects. t-PA@iRNP treatment showed the greatest effect of tumor

growth inhibition compared to free t-PA and iRNP individual treatment.

Chapter 5 describes that fibrinolytic t-PA as a new anti-tumor drug. t-PA treatment shows significantly anti-tumor effect in early and medium stages compared to control with negligible effects on the mouse body weight. In addition, fibrin deposition in colon tumor tissue was confirmed, t-PA depleted fibrin deposition, which improved classical activation macrophage M1 penetration with the inflammation promotion and cancer cells apoptosis properties in tumor tissues and inhibit tumor growth.

In an effort to improve the t-PA-installed nitroxide radical-containing, pH-sensitive self-assembled polyion complex nanoparticles (t-PA@iRNP) for ischemic stroke and cancer therapy, I have achieved four major advancements that provide a detailed insight and enhance the therapeutic performance of the system. First, the polyion complex afforded an optimized structure that stably loaded with low-dose t-PA and equipped with ROS-scavenging ability. Second, the synergistic effect of thrombolysis and antioxidant of t-PA@iRNP treatment was proved to significantly suppress an increase in infarct volume and improve neurological deficit in cerebral ischemia-reperfusion model mice *in vivo*. Third, t-PA@iRNP showed higher anti-tumor efficacy in a colon cancer mouse model, which was accompanied with decreased fibrin deposition, ROS level, tissue factor and attenuated NF-κB signaling in the tumors. Fourth, t-PA is potential as a new anti-tumor drug in the early and medium stage of tumor progression, which is anticipated to easily degrade fibrin deposition and increases the immune cells penetration in tumor tissues, providing a safe and specific inhibition of tumor growth. In summary, an advanced systemic configuration of t-PA-encapsulated nitroxide radical-containing, pH-sensitive self-assembled polyion complex nanoparticles for thrombolysis and anti-oxidant features in ischemia-reperfusion injury and anti-tumor efficacy in a colon cancer mouse model were successfully discovered, and these will strongly impact the new biomaterials field. Based on these results, further research into the clinical application of this system is warranted.

審　　査　　の　　要　　旨

〔批評〕

There are several question such as stability of t-PA@iRNP, fluorescent quenching mechanism, different between separate administration and complex, administration conditions, size and macrophage population, and She explained clearly about this. Finally, reviewing committee members and other audience understand well.

〔最終試験結果〕

2019 年　8 月　19 日、数理物質科学研究科学位論文審査委員会において審査委員の全員出席のもと、著者に論文について説明を求め、関連事項につき質疑応答を行った。その結果、審査委員全員によって、合格と判定された。

〔結論〕

上記の論文審査並びに最終試験の結果に基づき，著者は博士（工学）の学位を受けるに十分な資格を有するものと認める。